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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/754,468	01/04/2001	Patrick L. Iversen	0450-0033.30	3548

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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/754,468	IVERSEN, PATRICK L.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-6* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 1-12-04.

Claims 1, 4-6 and 13 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Applicant's arguments with respect to claims 1, 4-6 and 13 have been considered but are moot in view of the new ground(s) of rejection.

Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zyskind et al in view of the combination of McKay et al, Cook and Arnold, Jr. et al.

The claims are drawn to antisense oligomers which comprise at least 10 nucleotides in length specifically targeting the translational start codon for SecA of SEQ iD NO: 2, and which oligonucleotides are substantially uncharged, and comprise from 10 to 40 morpholino subunits, wherein adjacent subunits within each oligonucleotide are joined by uncharged (e.g. phosphor(di)amidate, carbonate, carbamate, amide linkages), or comprising charged phosphoramidate, phosphate or phosphorothioate linkages, which ratio of uncharged to charged linkages in the oligomers is at least 4:1.

Zyskind et al (USPN 6,228,579, filed 11-14-1997) teach antisense oligonucleotides comprising phosphorothioate internucleotide linkages, which oligonucleotides are effective to hybridize and inhibit the expression of a nucleic acid molecule encoding E. Coli sec-A of SEQ ID NO: 2 (See especially figure 11, col. 5,line 51-col. 6, line 20; col. 8, line 23-col. 9, line 40; col. 13, line 1- col. 18, line 30).

Zyskind does not teach oligonucleotides specifically targeting the translational start codon of SEQ ID NO: 2, nor a minimum ratio of uncharged to charged linkages within the oligonucleotide of 4:1.

McKay et al (USPN6,133,246,4-7-1999) teach antisense targeting various regions of a previously characterized target gene, including targeting the translational

start codon of the target gene of known nucleotide sequence (See esp. col. 5, line 65-col. 7, line 28; table 1 in col. 36 and table 2 in col. 37).

Arnold, Jr. et al (USPN 6,060,456 filed 10-27-1997) teach a relationship between incorporating various ratios of uncharged to charged linkages and antisense target binding, Rnase activation, antisense stability and cellular uptake (penetration), which charged groups include phosphodiesters and phosphorothioates and which uncharged groups include aryl- and alkyl-phosphonates, phosphoramidates and phosphotriesters, as well as alkyl- and aryl-phosphonothioates (see especially col. 2, line 42-col. 4, line 6).

Cook et al (USPN 6,239,265, filed 12-9-1998) teach the significance and distinguishing features of various internucleotide linkages (e.g. involving phosphorothioates, methylphosphates, phosphotriesters, phosphoramidates and phosphodiesters), which features includes solubility characteristics imparted to the oligonucleotides, nuclease resistance, Rnase activating abilities, facilitating cellular uptake and cellular penetration (See especially col. 1, line 36-col. 2, line 14; claims 1-8).

It would have been obvious to one of ordinary skill in the art to utilize antisense oligonucleotides which target and inhibit the expression of E. Coli sec-A, because the polynucleotide sequence of E. Coli sec-A (SEQ ID NO: 2) and the utilization of antisense which target and inhibit the expression of sec-A as an antibacterial agent had been taught previously by Zyskind et al. One of ordinary skill in the art would have been motivated to target particular regions of the target gene of known sequence, including the initiation region, because McKay teaches the routine experimentation of designing and testing antisense oligonucleotides for the different regions spanning a known target

gene, including the initiation region, whereby expression of the target gene is obtained. One of ordinary skill in the art would have expected that antisense of at least 10 nucleotides specifically targeting the initiation codon region of SEQ ID NO: 2 would inhibit the expression of SEQ ID NO: 2 in vitro. Targeting the initiation region of a known target gene with antisense of at least 10 nucleotides has been taught by many in the art, including McKay and it would require routine experimentation to target this region to inhibit SEQ ID NO: 2 in vitro. It would have been obvious to one of ordinary skill in the art to incorporate mixed internucleotides linkages, including uncharged and charged linkages, because such mixed linkages had been incorporated into antisense oligonucleotides previously by both Arnold and Cook because a combination of charged and uncharged linkages impart a combination of useful properties for antisense oligonucleotides such as enhanced target binding, stability from nuclease degradation, Rnase activation and cellular uptake, which properties have been exploited previously by Zyskind et al, Arnold and Cook. One of ordinary skill in the art would have been motivated to design antisense oligonucleotides comprising both charged and uncharged oligonucleotides in order to enhance stability, modulate solubility, enhance cellular uptake, target binding and Rnase activation. One of ordinary skill in the art would have expected that a ratio within the range of 3-5:1, uncharged to charged linkages would be suitable for enhancing target binding and cellular uptake, because such a range was utilized by Arnold (e.g. see figure 7 and col. 3, line 62-col. 4, line 6 of Arnold).

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claim 13 appears free of the prior art of record, but is objected to for depending from a rejected claim.

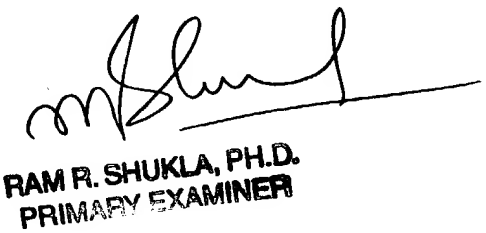
Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

JZ

4-1-04